PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Staats et al.

Serial No.: Not Assigned Group Art Unit:1647

Filed: Herewith Docket No.: 180/102/2

For: SUBSTANTIALLY NON-TOXIC BIOLOGICALLY ACTIVE MUCOSAL ADJUVANTS IN VERTEBRATE SUBJECTS

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INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

In accordance with 37 C.F.R. 1.56, 1.97, and 1.98, applicants' undersigned attorney brings to the attention of the Patent and Trademark Office the following references. Forms PTO/SB/08A and PTO/SB/08B are attached hereto.

Copies of the cited documents are of record in the file history of U.S. Patent Application Serial No. 09/168,910 filed on October 8, 1998. The above-captioned application claims priority to U.S. Patent Application Serial No. 09/168,910 under 35 U.S.C. § 120, and as per 37 C.F.R. § 1.98, no copies of these cited documents are believed to be required.

U.S. Patent No. 4,935,343 to Allison et al. discloses novel monoclonal antibodies which bind to Interleukin-1 beta and do not bind to Interleukin-1 beta.

U.S. Patent No. 5,008,374 to Nakai et al. discloses polypeptides with 157-9 aminoacid units have the same sequence as that in interleukin -1 alpha except that Asn at 36 position and/or Cys at 141 position is deficient or replaced by Ser.

U.S. Patent No. 5,266,311 to Cerratti et al. discloses a method of cloning and an expression of DNA segments encoding bovine IL-1α, and processes for producing purified bovine IL-1α as a product of recombinant cell culture.

U.S. Patent No. 5,334,379 to Pillai et al. discloses a process for cytonine and hormone carriers for conjugate vaccines.

U.S. Patent No. 5,342,614 to Nakai et al. discloses a method of treating arthritis or inflammation with IL-1β or derivatives thereof.

U.S. Patent No. 5,342,615 to Nakai et al. discloses a method for treating arthritis or inflammation with IL-1α or derivatives thereof.

U.S. Patent No. 5,371,204 to Nakai et al. discloses a gene that encodes for polypeptides of IL-1α.

U.S. Patent No. 5,437,988 to Bellini et al. discloses an expression and secretion of mature human beta interleukin-1 in *Bacillus subtilis* and means and method for its achievement.

U.S. Patent No. 5,474,899 to Lisi discloses a selective, sensitive, and highly reliable immunoassay for detecting human IL-1 beta in cultured mononuclear cells or human body fluids.

U.S. Patent No. 5,543,140 to Nakai et al. discloses a method and use of IL-1α.

U.S. Patent No. 5,702,698 to Nakai et al. discloses methods of use of IL-1α.

U.S. Patent No. 5,728,571 to Velati Bellini et al. discloses an expression and secretion of mature beta interleukin-1 in *Bacillus subtilis* and means and methods for its achievement.

U.S. Patent No. 5,210,072 to Chedid et al. discloses muramyl dipeptide derivatives.

U.S. Patent No. 5,206,014 to Nencioni et al. discloses a synthetic nonpeptide for use as an adjuvant.

WO 88/06843 to Cerreti et al. discloses cloning and expression of nucleotide DNA segments encoding bovine I-1B, and processes for producing purified bovine IL-1B as a product of recombinant cell culture.

WO 91/01143 to Pillai et al. pertains to interleukins-containing vaccine compositions, comprising a mixture of antigen and an adjuvant amount of an interleukin absorbed onto a mineral in suspension and a preservative.

WO 91/13986 to Maliszewsk discloses that the DNA sequence and derived amino acid sequence of porcine interleukin-1 alpha (pIL-1alpha) are new.

WO 92/03574 to Andrews et al. discloses a process for identifying nucleotide sequences coding for a polypeptide exhibiting specific ruminant cytokine or cytokine receptor activity.

WO 94/00491 to Bartfai et al. discloses the interleukin1-β deletion mutant, which has a quasi conserved sequence of three aminoacids deleted from the amino acid sequence of an endogenous mammalian Interleukin-1β.

NL 93/01929 to Billiau discloses new DNA fragments code for porcine interleukin 1-beta or polypeptides with modified versions of this sequence which do not negatively affect their biological activity. (English Abstract Only).

EP 810285 to Dorssers et al. discloses that mutants of hIL-3 are provided having deletions covering virtually the complete coding region of hIL-3, while retaining their biological activity.

EP 761688 to Landon discloses a method of producing a mixture of polyclonal antibodies, the mixture including polyclonal antibodies which bind to at least two cytokines comprising the steps of (1) administering to an animal a sufficient amount of each a cytokine immunogen to provide an immune response to each of the cytokine immunogens: (2) allowing an immune response to develop to each of the cytokine immunogens; and (3) removing blood from the animal.

WO 96/07673 to Larsen et al. discloses the use of three novel peptides for the manufacture of a composition for the treatment of diseases, the pathogenesis of which is related to the decreases production and/or function of immuno-stimulating mediators, especially cytokines.

EP 353516 to Velati Bellini et al. discloses a method for the preparation of recombinant human beta interleukin-1 in the homogenous form by the purification, in a single chromatographic step, of the soluble fraction obtained by the breaking of engineering Bacillus cells.

JP 05-244990 to Muraguchi et al. discloses that the subject antibody, prepared by using rat interleukin-1s(IL-1s) as an immunogen, has specific reactivity toward rat IL-1-α or rat IL - 1β and is useful for high-sensitivity immunoassay, etc., for the rat IL-1s. (English Abstract Only).

JP 63-258595 to Omoto et al. discloses a monoclonal antibody having specific reactivity to human interleukin 1α or human interleukin 1-β. (English Abstract Only).

Publication by Sarkar, "Drug Metabolism in the Nasal Mucosa," Pharm. Res. , p. 1-9, (1992).

Publication by Pontiroli et al. entitled "Nasal Administration of Glucagon and Human Calcitonin to Healthy Subjects: A Comparison of Powders and Spray Solutions and of Different Enhancing Agents", European Journal of Clinical Pharmacology, (1989), Vol. 37, pp. 427-430.

Publication by Elson et al. entitled "Mucosal Adjuvants", Handbook of Mucosal Immunology, P.L. Ogra et al. eds., Academic Press, Inc., San Diego, (1994), pp. 391-402.

Publication by Reiss, T. and Strauss, E. entitled "Vaccines -Patenting Dynamics of a Powerful Healthcare Tool", Exp. Opin. Ther. Patents, (1998), Vol. 8, No. 8, pp. 951-958.

Publication by Elson entitled "Cholera Toxin as a Mucosal Adjuvant", Mucosal Vaccines, H. Kiyono et al. eds., Academic Press, New York, (1996), pp. 59-72.

Publication by Jenkins entitled "Mucosal Vaccine Delivery", Exp. Opin. Ther. Patents, (1999), Vol. 9, pp. 255-262.

Publication by Lillard et al. entitled "Lymphotactin Acts as an Innate Mucosal Adjuvant", J. Immuno., (February 15, 1999), Vol. 162, No. 4, pp. 1959-1965.

Publication by MRSNY entitled "Adjuvants and Delivery Issues Related to Immunization: A Survey of the Recent Patent Literature", J. of Drug Targeting, (1998), Vol. 6, No. 4, pp. 243-249.

Publication by Giannarini et al., "Decrease of Allergen-specific T-cell Response Induced by Local Nasal Immunotherapy", Vol. 28, Clinical and Experimental Allergy,

pp. 404-412 (1998) discloses that the allergen specific immunotherapy is recognized as highly effective in the treatment of patients with severe allergic rhinitis and/or asthma.

Publication by Pockley et al., "*In Vivo* Adjuvant Effect of Interleukins 5 and 6 on Rat Tear IgA Antibody Responses", Vol. 73, Immunology, pp. 19-23 (1991) discloses the linkage of the lacrimal compartment to the mucosal immune network supported by evidence that IgA-bearing cells from mesenteric lymph nodes and glandular mucosal tissue preferentially seed lacrimal glands in a similar manner to other components of the mucosal immune system.

Publication by O'Hagan, "Recent Advances in Vaccine Adjuvants for Systemic and Mucosal Administration", Vol. 49, J. Pharm Pharmacol, pp. 1-10 (1997) discloses that although vaccines produced by recombinant DNA technology are safer that traditional vaccines, based on attenuated or inactivated bacteria or viruses, they are often poorly immunogenic.

Publication by Kramer et al., "Cytokine Mediated Effects in Mucosal Immunity", Vol. 73, Immunology and Cell Biology, pp. 389-396 (1995) discloses that the predominance of IgA antibodies in mucosal sites reflects a combination of high rate IgA isotype switching among precursor cells in induction sites, their selective localization in mucosal effector tissues and vigorous proliferation of these cells after extravasation.

Publication by Nash et al., "Recombinant Cytokines as Immunological Adjuvants", Vol. 71, Immunology and Cell Biology, pp. 367-379 (1993) describes the bacterial expression and purification of bioactive recombinant ovine interleukin-2 (rovIL-2), interleukin-1α (rovIL-1α) and tumour necrosis factor α.

Publication by Lin et al., "Present Status of the Use of Cytokines as Adjuvants with Vaccines to Protect Against Infectious Diseases", Vol. 21, Clinical Infectious Diseases, pp. 1439-49 (1995) discloses that vaccine adjuvants are expected to play an important role in enhancing the immunogenicity of existing and new-generation vaccines against infectious diseases.

Publication by Li et al., "Nasal Tolerance to Experimental Autoimmune Myasthenia Gravis: Tolerance Reversal by Nasal Administration of Minute Amounts of

Interferon-γ", Vol. 87 Clinical Immunology and Immunopathology, pp. 15-22 (1998) discloses a tolerance to B cell-mediated experimental autoimmune myasthenia gravis (EAMG), an animal model for myasthenia gravis (MG) in humans, can be achieved by nasal administration of the autoantigen acetylcholine receptor (AChR).

Publication by Marinaro et al., "Oral but Not Parenteral Interleukin (IL)-12 Redirects T Helper 2 (Th2)-type Responses to an Oral Vaccine Without Altering Mucosal IgA Responses", Vol. 185, No. 3, J Exp. Med., pp. 415-427 (February 3, 1997) discloses that the mucosal adjuvant cholera toxin (CT) induces T helper type 2 (Th2) responses with systematic IgG1, IgE and mucosal secretory IgA (S-IgA) antibodies (Abs).

Publication by Xiao et al., "Suppression of Acute and Protracted-relapsing Experimental Allergic Encephalomyelitis by Nasal Administration of Low-dose IL-10 in Rats", Vol. 84, Journal of Neuroimmunology, pp. 230-237 (April 15, 1998) reports that nasal administration of the Th2 cell-related cytokine interleukin-10 (IL-10) at concentrations of 1.5 mu g/rat and 15 mu g/rat, suppressed clinical signs of acute experimental allergic encephalomyelitis (EAE) in Lewis rats and prevented the development and relapse of protracted-relapsing EAE (PR-EAE) in DA rats. (Abstract Only)

Publication by Fujimara et al., "Effect of Thromboxane A2 Antagonists on Bronchial Hyperresponsiveness Induced Immediately after Interleukin-8 Inhalation in Guinea-pigs", Vol. 122, British Journal of Pharmacology, pp. 1015-1020 (1997) discloses various cytokines presumed to be involved in the signalling between cells and to contribute to the pathophysiology of bronchial asthma.

Publication by Callard et al.,"The Cytokine Facts Book", Academic Press, Harcourt and Co., Publishers, pp. 241 (1994).

Publication by Abraham et al., "Intranasal Immunization with Liposomes Containing IL-2 Enhances Bacterial Polysaccharide Antigen-Specific Pulmonary Secretory Antibody Response", Journal of Immunology, Vol. 149, No. 11, pp. 3719-3726 (1992).

Publication by Gao et al., "BHV-1 Glycoprotein 1 and Recombinant Interleukin 1B Efficiently Elicit Mucosal IgA Response", Vaccine, Vol. 13, No. 9, pp. 871-877 (1995).

Early passage of the subject application to issue is earnestly solicited.

Although it is believed that no fee is due, the Commissioner is hereby authorized to charge any deficiencies of payment associated with the filing of this Information Disclosure Statement to Deposit Account No. **50-0426**.

Respectfully submitted,

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Enclosures